Sackett, et al. (*21*) have demonstrated a clear dose-relationship between cigarette smoking and the severity of aortic atherosclerosis at autopsy. Their study of 1,019 consecutive autopsies, on patients who had been interviewed about their smoking habits prior to death, showed a significant increase in the severity of aortic atherosclerosis with increasing use of cigarettes, measured both by intensity and by duration of smoking.

An autopsy study from Russia by Avtandilov, et al. (*3*) demonstrated a significantly greater degree of atherosclerosis in the coronary arteries of smokers than in those of nonsmokers.

Viel, et al. (*28*) have reported on the severity of coronary atherosclerosis at autopsy of 1,150 men and 290 women who died violent deaths in Chile. Information on smoking habits was available on 566 men. The authors report no relationship between atherosclerotic lesions and the use of tobacco. The degree of atherosclerosis was expressed as the percentage of the surface of the intima of the left anterior descending coronary artery covered by fatty streaks and fibrous plaques. An examination of the data presented in graphic form indicates that the moderate and heavy smokers appear to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.

A study by Astrup was reviewed in the 1968 Report (*27*). This study showed that in rabbits on a high cholesterol diet, chronic carbon monoxide exposure has a marked atherogenic effect.

Kjeldsen, et al. (*15*) compared the vascular pathology in rabbits fed a high cholesterol diet and maintained in an hypoxic atmosphere (10 percent oxygen) with that in rabbits exposed only to the high cholesterol diet. The authors demonstrated that hypoxia leads to an increase in the degree of plaque formation in the coronary arteries and in the amount of visible aortic atheromatosis, as well as to an increase in the aortic content of cholesterol and triglycerides. In addition, the hearts of the hypoxic animals showed marked perivascular xanthomatosis, often infiltrating the surrounding myocardium. In summarizing this experiment and their previous findings of increased atheromatosis in hypercholesterolemic rabbits subjected to high carboxyhemoglobin (COHb) levels, the authors (*2*) state that tissue hypoxia seems to be an important factor in initiating these lesions, regardless of the manner in which the hypoxia is produced. Although the COHb levels in the rabbits and the degree of hypoxia were much higher than that experienced by human smokers, these results suggest a mechanism by which smoking might contribute to atherosclerosis.

Hass, et al. (*12*), extending studies reviewed in the 1968 Report (*27*), have demonstrated that the administration of injections of nico-

tine to hypercholesterolemic rabbits who are also given vitamin D enhances the peripheral atheromatous calcific arterial disease which is produced by the combination of hypercholesterolemia and vitamin D administration. The addition of nicotine to the regimen also resulted in the frequent occurrence of thromboarteritis in the distal calcified arteries of cardiac and skeletal muscle, and of the smooth muscle of the gastrointestinal tract. The nicotine effect was reproduced by substituting appropriate dosages of adrenalin for nicotine and abolished by adrenalectomy.

Lellouch, et al. (*16*) have reported that the administration of a mono-amine oxidase (MAO) inhibitor to rabbits on a regimen of daily nicotine injections significantly reduced the number of animals who developed fibrotic lesions of the aorta in response to nicotine. Further work is in progress to elucidate the mechanism of the MAO effect.

Evidence presented in this and previous reports suggests that cigarette smoking promotes atherosclerosis.

Thrombus Formation and Blood Flow

Hess, et al. (*13*) discovered aggregations of platelets, erythrocytes, fibrin, detached epithelial cells, and some as yet unidentified cells on the aortic and carotid walls of rabbits subjected to cigarette smoke.

The discovery of a plasma factor which increases the *in vitro* synthesis of fibrinogen by human liver biopsies has been reported by Pilgeram, et al. (*20*) in older patients who have recovered from myocardial infarction. This factor has been tentatively identified as free fatty acid (FFA). The authors state that the association between FFA and fibrinogen synthesis may provide the link between hyperlipemia and clotting. Cigarette smoking causes an increase in FFA through its stimulation of catecholamine release.

Several recent studies have begun to elucidate the role which changes in blood viscosity and certain features of the microcirculation might play in the development of atherosclerosis and coronary heart disease.

Dintenfass (*7*) has suggested that myocardial infarction and coronary thrombosis may be the result of a number of factors, separate or interrelated, all leading to a high viscosity of the blood. These factors may affect the migration and adhesion of platelets, the volume of plasma, and the rigidity of the red blood cell. Phenomena leading to high blood viscosity may occur in focal areas leading to occlusion of small vessels, resultant ischemia, and an infraction of either subclinical or catastrophic proportions, depending on the location and number of vessels involved. Dintenfass also believes that an increase in blood

viscosity precedes the clinical manifestations of the high blood viscosity syndrome and that the increased blood viscosity seen in post myocardial infarct patients is a reflection of the etiology rather than the effect of the disease.

Local hypoxia leading to an increase in the rigidity of the blood cell might be produced by cigarette smoking through the increase in COHb. Platelet adhesiveness is increased by smoking, probably secondary to the release of catecholamines (*27*).

In a study of 50 white males with myocardial infarcts and 40 controls, Stables, et al. (*23*) found that the patients with myocardial infarct had a mean hematocrit level significantly higher than that of the controls. Studies of blood volume indicated that a reduction in plasma volume rather than an increase in red cell mass among the myocardial infarct patients accounted for the elevated hematocrit.

Carbon Monoxide

Several reviews of the pathophysiology of exposure to carbon monoxide (CO) have appeared recently. These are pertinent to the discussion of the relationship of smoking to health, since cigarette smoke contains amounts of CO sufficient to cause a COHb level of 5 to 10 percent in the smoker, depending on the amount smoked and degree of inhalation (*9*, *10*).

Bartlett (*4*) has pointed out that because the absorption of CO from the ambient environment is dependent upon the concentration of CO in the environment as contrasted to that in the blood, smokers with a COHb level of 5 percent will not absorb CO from inspired air unless the concentration of CO in the air exceeds 30 parts per million. However, he also states that because the excretion of CO between cigarettes will be lower in CO polluted air, the smoker will have a higher long-term average COHb level in a polluted environment. Patients with heart disease may be particularly susceptible to the hypoxic burden caused by the presence of COHb.

Goldsmith, et al. (*10*) have stated that for the U.S. urban population, cigarette smoking is probably the most important cause of increased COHb above the endogenous level produced by heme catabolism, followed by automobile exhaust, occupational sources, and home heating and cooking devices, in that order.

Although Dinman (*6*) minimizes the importance of the effect of CO levels of 5 to 10 percent on the myocardium, he states that a shortcoming in his approach is that focal areas of myocardial ischemia are not reflected in the determination of oxygen saturation made from samples of blood taken from the coronary sinus. Such areas of ischemia might be important in initiating fatal arrhythmias. Levels of COHb

which decrease further the oxygen supply to the ischemic myocardium might be readily provided by cigarette smoking.

Eliot, et al. (*8*) have reported effects of cigarette smoking on the oxygen affinity of hemaglobin independent of the presence of CO. Their results suggest that cigarette smoking may have both acute and chronic effects on oxygen affinity which differ in direction. The authors caution, however, that the *in vivo* oxygen affinity of hemoglobin may be different from that implied by the static equilibrium data. Further research is in progress.

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CHAPTER 2

Smoking and Chronic Obstructive Bronchopulmonary Disease

Contents

SMOKING AND CHRONIC OBSTRUCTIVE BRONCHOPULMONARY DISEASE

Summary

Additional evidence which supports the previous judgment of a cause and effect relationship between cigarette smoking and chronic obstructive bronchopulmonary diseases, especially chronic obstructive bronchitis, continues to accumulate from both the United States and abroad. New work has been published in the past year which provides additional information on the possible mechanisms by which cigarette smoking can lead to the production of pulmonary emphysema. These mechanisms include collapse of small airways, changes in pulmonary surfactant, impairment of pulmonary clearance, disruption of the normal architecture of the bronchial epithelium, and obstruction of capillaries of the bronchi and alveoli. At present, there is no unified hypothesis for the pathogenesis of pulmonary emphysema; however, the pathogenetic mechanisms may involve more than one component of lung tissue. Epidemiological and laboratory evidence supports the view that cigarette smoking can contribute to the development of pulmonary emphysema in man.

Chronic Bronchitis

Cigarette smoking is the most important cause of chronic bronchitis. In the past year, studies from various countries have appeared in the literature reconfirming this association. In studies of populations of working men in Italy (*15*), the Netherlands (*6*), England (*16, 35*) and the United States (*9*), smokers were found to have a significant increase in either incidence or prevalence of chronic bronchitis as compared to the nonsmokers. Studies of populations from rural and urban Sweden (*31*) and rural Australia (*25*) produced similar findings. A South African study (*45*) demonstrated decreased forced expiratory volumes (FEV_1) and peak expiratory flow rates (PEFR) with increased tobacco consumption, even in those who did not have chronic bronchitis.

Prevalance of Chronic Obstructive Bronchopulmonary Disease

The prevalence of chronic obstructive bronchopulmonary disease is probably underestimated. In a study of death certificates, Moriyama, et al. (*39*) have reported that chronic obstructive bronchopulmonary disease is often omitted as a contributing cause of death. Mitchell, et al. (*38*) also found that the disease often goes unreported. Barach, et al. (*5*) maintain that much of the reported increase in the prevalence of chronic obstructive bronchopulmonary disease can be accounted for by better diagnosis. However, Barach, et al. base their statement on the supposition that the rising death rates from chronic obstructive bronchopulmonary disease are incompatible with the fact that many people are giving up smoking. However, it should be pointed out that chronic obstructive bronchopulmonary disease associated with cigarette smoking may be the result of many years of exposure to cigarette smoke and the mortality rates from bronchitis and emphysema would not reflect large-scale smoking cessation for some time to come. Burrows (*10*) has pointed out that the effects of cessation of smoking on the course of already existing chronic obstructive bronchopulmonary disease may be difficult to assess, since it may be that those who are disabled by severe disease tend to stop smoking more often than those who have milder forms of the disease. The beneficial effects of cessation of smoking could thus be masked.

Pulmonary Emphysema

Many agents appear to contribute to the development of emphysema, but epidemiological and experimental evidence indicates that cigarette smoking is the most important agent in the development of pulmonary emphysema in man. Mention of the theories of pathogenesis of pulmonary emphysema, long the subject of debate among medical scientists (*1*, *34*, *46*, *47*, *48*), may help to serve as background for the presentation of recent research on the role of cigarette smoking in the development of emphysema.

Two major theories of the pathogenesis of chronic obstructive pulmonary emphysema have been proposed. One theory states that the primary lesion of emphysema is vascular and involves obstruction either by thrombosis or by endarteritis of the pulmonary or bronchial arterial branches. The resultant loss of nutrient supply is thought to result in ischemic necrosis of the alveolar wall and septa. The other major theory states that chronic obstructive pulmonary emphysema results from the direct effect of toxic inhalants on the pulmonary tissue, in the areas of the terminal bronchioles and alveoli. According to this theory, changes seen in the pulmonary and bronchial vessels are

secondary to the destruction of nonvascular tissue. It may well be that the pathogenesis of pulmonary emphysema can involve several mechanisms and that both of these theories may be applicable but not mutually exclusive (*44*).

Experimental Studies in Man

Anderson, et al. (*2*) have reported preliminary results which indicate that cigarette smoking causes acute changes in the ventilation/perfusion relationships of the lung and that patients with chronic obstructive bronchopulmonary disease appear to be particularly liable to these changes. In some patients the changes are predominantly in perfusion, a finding which lends support to the vascular theory of pulmonary emphysema. In other patients, the changes are predominantly in ventilation, a finding which lends support to the theory of the direct effect of inhalants in the pathogenesis of pulmonary emphysema.

Anthonisen, et al. (*3*) investigated pulmonary function in 10 male smokers with clinically mild chronic bronchitis, all of whom had smoked cigarettes for at least 20 years. Besides the usual pulmonary function tests, these investigators employed a technique for the assessment of regional pulmonary function using radioactive xenon. Despite the fact that overall pulmonary function was nearly normal in several patients, all had decreased ventilation and depressed ventilation/perfusion ratios in some lung regions, with the basal areas being those most commonly affected. The author suggested that significant disease in the peripheral airways may exist in patients whose chronic bronchitis is clinically mild and who show no present impairment of ventilatory capacity. The radioactive xenon test may reveal severe compromise of the overall gas exchange when usual studies of ventilatory capacity do not reveal impairment. These changes in the distal airways may become more significant clinically as the patient ages, since aging has been shown to be associated with a diminution in the compliance of the lung (*29*). Peters, et al.(*40*) have reported that the lower flow rates found among college students who smoke, especially at lower lung volumes, may reflect disease in the small airways. The diminution in flow in these subjects was approximately proportionate to the total lifetime number of cigarettes smoked.

Fullmer, et al. (*22, 23, 24*) have found a high prevalence of Curschmann's type spirals in the sputum of cigarette smokers. The easily recognized spirals consist of inspissated mucus and are casts of the lumens of small bronchioles. These spirals were found in the sputum of 23 of 24 cigarette-smoking women and in 97 of 100 cigarette-smoking men. The total number of spirals on four slides prepared for

microscopic examination varied from 0 to 500. Six of 10 ex-smokers had spirals in their sputum, but the number of spirals was reduced to a total of 10 or less on four slides. A nonsmoking control group exposed to cigarette smoke at work showed a low prevalence of spirals, while a control group of nonsmokers not exposed to cigarette smoke at work showed no spirals in their sputum. Fullmer has suggested that Curschmann's spirals may play a role in the development of emphysema by producing obstruction at the bronchiolar level. The spirals may also allow prolonged contact between admixed inhalants including cigarette smoke and the bronchiolar walls. A study of the presence of spirals in the sputum of a group of nonsmoking asthmatic bronchitics would be useful in an attempt to determine whether the presence of spirals is a direct result of exposure to cigarette smoke, or is a characteristic of the sputum of bronchitics, whatever the cause of their bronchitis.

Studies in Animals

Frasca, et al. (*17*, *18*) have reported on electron microscopic observations of the bronchial epithelium of dogs exposed to cigarette smoke by active inhalation through a tracheostoma. The epithelium of a dog exposed to 44 days of smoking by methods previously described by Cahan, et al. (*11*) showed a proliferation of goblet cells and a partial loss of cilia in the surface lining cells. After 420 days of exposure to cigarette smoke, the number of cell layers in the epithelium was found to be twice that of the nonsmoking dogs. Goblet cells and ciliated columnar cells were no longer present; instead, the surface was lined with columnar and cuboidal cells with stubby projections in place of cilia. Mitotic figures were frequently observed in the basal cells. These findings may be relevant to carcinogenesis as well as to the development of chronic obstructive bronchopulmonary disease.

Tyler (*49*) and McLaughlin, et al. (*37*) have studied the physiology and morphology of pulmonary emphysema in the horse. The lung of the horse has been reported to be similar in subgross anatomy to that of man (*36*). They have studied both the spontaneous disease, one of the several causes of the syndrome known as "heaves," and a similar but not identical pulmonary disease induced by the injection of chlorpromazine or of styrene beads into the bronchial arterial circulation. Their findings of obstructive lesions in the bronchial circulation and of accompanying emphysematous changes in the pulmonary parenchyma provide indirect support of a vascular theory of emphysema. Ricketts, et al. (*41*) were unable to produce emphysematous lesions in sheep by occlusion of the bronchial artery; however, species differences in the distribution of this vessel may be an important factor

in both experimental and spontaneous disease. The bronchial artery in the horse is reported to supply the alveolar septa, whereas in the sheep it is reported to reach only as far as the terminal bronchioles (*36*).

A pulmonary disease similar histologically to pulmonary emphysema in man appears spontaneously in certain populations of rabbits (*12*). Boatman, et al. (*8*) have studied this disease by means of the electron microscope. Three of their findings which tend to support the theory that the disease is primarily vascular in origin are as follows: loss of capillary endothelium, partial or complete filling of the capillary lumens with collagen, and frequent recanalization of the damaged capillaries.

Freeman, et al. (*19*, *20*, *21*) have investigated the effect of chronic exposure of rats to varying concentrations of nitrogen dioxide (NO_2), a gas which is found in cigarette smoke and in industrially polluted air. These investigators showed that the exposure of rats over their lifetime of 2 to 3 years to concentrations of 2 (± 1) parts per million of NO_2 resulted in reduction in cilia of the bronchial epithelium, a reduction in normal exfoliation, and the appearance of unidentified crystalloid inclusions. Exposure for only 16 weeks to a higher concentration of 4 (± 1) parts per million led to hypertrophy of the epithelium of the terminal bronchioles. Rats exposed to concentrations varying from 10 (± 1) to 25 (± 2) parts per million of NO_2 developed large, heavy, nonedematous lungs accompanied by dorsal kyphosis. The increase in weight of the lung was shown to be caused by widespread hypertrophy of the respiratory epithelium, especially in the bronchioles closely associated with alveolar ducts and in the terminal bronchioles. Hypertrophy of the bronchial epithelium and accumulation of amorphous proteinaceus material, fibrin strands, and macrophages resulted in narrowing of the lumens of the terminal bronchioles at their junctions with the alveolar ducts. Focal hypertrophy of alveolar epithelium appeared to be associated with compression of alveolar capillaries. The airspaces of the lung were increased in volume.

Other investigators have also reported an increase in alveolar size in rodents exposed to NO_2. Blair, et al. (*7*) exposed mice to 0.5 parts per million of NO_2 for 6, 18, or 24 hours each day. The animals were exposed to NO_2 for periods varying from 3 to 12 months; the degree of change in the pulmonary histology appeared to increase with increased total length of exposure. Besides producing enlarged alveoli, exposure to NO_2 also produced early bronchiolar inflammation with a concomitant reduction in the size of the distal airways.

Other Studies

In a recent extensive review of the nature and role of pulmonary surfactant, Scarpelli (*43*) states that the lowering of surface tension produced by the action of cigarette smoke on surfactant may predispose to the development of emphysema.

Cigarette smoke contains powerful ciliostatic agents (*50*, *51*, *52*) which can interfere with pulmonary clearance. Components of both the particulate and the gaseous phases adversely affect ciliary activity. Dalhamn, et al. (*14*) have pointed out that in assessing the effect of one or another of the components of cigarette smoke on ciliary activity in various animal systems particular attention must be paid to the level of exposure, since at different dosages the particulate and gaseous phases have different relative effects on ciliary activity. Other recent work by Dalhamn, et al. (*13*) has further clarified the extent to which certain components of cigarette smoke are retained in the human lung and includes the observation that retention of gaseous components depends in part on adsorption of the gases on particulate matter.

Ballenger, et al. (*4*) have indicated that the *in vitro* ciliostatic effects of oxidized nicotine are enhanced by prior infection of the tissue explants with Influenza B Virus.

Holma (*30*) has reported that cigarette smoke has acute depressant effects on pulmonary clearance in living rabbits.

Recently, observations have been published on the metabolism and function of the pulmonary alveolar macrophage which, together with mucus transport, performs the function of ridding the lung of both inanimate particles and bacteria. Green (*27*) points out the importance of the alveolar macrophage in pulmonary clearance of infectious agents. He has also observed a deleterious dose-response effect of cigarette smoke on the phagocytic activity of the macrophage and suggests that this effect may be related to the development of chronic bronchopulmonary disease.

In another paper, Green (*26*) found that the cytotoxic activity of cigarette smoke on pulmonary macrophages may be inhibited by glutathione and cysteine. Izard (*32*) observed that the gaseous phase of cigarette smoke or one of its components, acrolein, inhibited the multiplication of cultures of *Dunaliella bioculata* and also observed that the addition of cysteine to the medium protected against these effects of acrolein.

Heise, et al. (*28*) have reported that rabbit pulmonary alveolar macrophages secrete lysozyme into a culture medium. Lysozyme may be active in the clearance of bacteria from the lung.

Roque, et al. (*42*) found a decrease in the activity of oxiodoreductases and hydrolases in the alveolar macrophages of smokers. They

also found that the reduction in these enzymes was directly proportional to the amount of stored fluorescent material present in the macrophages. This material is thought to originate in tobacco smoke. Roque, et al. suggested that the tobacco smoke may have induced abnormalities in the mitochondria of the macrophage.

Kilburn (*33*) theorizes that the pathogenesis of chronic obstructive bronchopulmonary disease is related to the failure of macrophages to be cleared from the alveoli and bronchioles because of impaction of mucus. He suggests that dissolution of the cells exposes the alveoli and bronchioles to damaging enzymes and to the phagocytosed particles contained in the macrophage.

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